Notice of Allowability	Application No.	Applicant(s)	
	09/723,722	ANDERSON ET AL.	
	Examiner	Art Unit	
	Malgorzata A. Walicka	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *Feb. 08, 2006*.

2. ☒ The allowed claim(s) is/are *1, 15, 18, 22 -25, 31, 33-34, 36 and 133-135*.

3. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

4. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☒ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☒ Information Disclosure Statements (PTO-1449 or PTO/SB/08), Paper No./Mail Date 12/08/2004
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application (PTO-152)
6. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
7. ☒ Examiner's Amendment/Comment
8. ☒ Examiner's Statement of Reasons for Allowance
9. ☒ Other *See Continuation Sheet*.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application February 6, 2006, after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office Action has been withdrawn pursuant to 37 CFR 1.114. Response to Advisory Action –Amendment under 37 CFR1.116 filed Feb. 06, 2006 containing amendment to the claim is acknowledged. Claim 1 has been amended; and claims 29 and 30 have been canceled. Claims 1, 15, 18, 22-25, 31, 33-34, 36, and 132-134 are pending and the subject of this action.

DETAILED ACTION

1. Withdrawal of rejections under 35 USC section 103

The rejection of claims 1, 15, 18 and dependent claims 22 and 132-134 was maintained in the Advisory Action of January 19, 2006. The examiner's position was the claims were unpatentable over US Patent 6,420,534, issued to Gurney et al., with priority to the provisional application 60/101,594 filed Sept. 24, 1998, in view of the common knowledge in molecular biology and in the field of aspartyl proteases as exemplified by the review article by Tang J. et al. (Evolution in Structure and Function of Aspartyl Proteases, Journal of Cellular Biochemistry, 1987, 33, 53-63). It was argued that Tung et al. would enable truncation of the first 45 amino acid of SEQ ID NO: 2 for production of a recombinant beta-secretase.

This rejection is now withdrawn for the reasons presented below.

The instant application claims benefits of provisional applications 60/119,571 filed 02/10/1999, 60/138,172 filed 06/15/1999 and 60/114,408 ('408) filed 12/31/1998. Reconsideration of the content of all provisional applications, Gurney's application 60/101,594, and the state of art on eukaryotic aspartyl proteases (including those presented in examiner's references, PTO form 892, copies attached) leads to the following conclusions.

Applicants would have been not motivated to truncate SEQ ID NO: 2 by removing the first 45 amino acid, because the purified beta secretase enzyme they obtained from human brain tissue had as its N-terminus a polypeptide of 22 amino acids consisting of amino acids residues 46-66 of SEQ ID NO: 2 (the result obtained by N-terminal amino acids sequencing). The 22 amino acid sequence was translated into nucleotide sequence and used for RT—PCR of mRNA form human brain. This was the first step in obtaining the full cDNA of SEQ ID NO: 1- see Fig. 4 of '408 - enclosed. Thus, the protein of amino acid sequence starting with amino acids 46 was the very protein Applicants have their hands on. Gurney et al have chosen different approach to obtain cDNA and amino acid sequence of human beta secretase identified by SEQ ID NO: 2. They scan gene data bases for the active site motif characteristic of aspartyl proteases, the sequence DTG or DSG, which is repeated twice in human aspartyl proteases. Thus, as indicated above, Gurney did not have in their hands a protein that starts with amino acid residue 46 and is beta secretase, neither they taught that the beta secretase of their SEQ ID NO: 6, instants SEQ ID NO: 2, when recombinantly

produced in human cells starts with amino acids residues 22, 46, 58, or 63 of SEQ ID NO: 2, what Applicants pressened in the next provisional applications.

The Applicants present in Fig 8 of '408, sequence alignment of human cathepsin D, E and pepsin of the atlantic cod, and their own human-beta secretase of SEQ ID NO: 2. The aligned sequences are the most maching sequences in bioinformatics search; they are about 30% identical one to each other. However, the state of art teaches that human cathepsin D has a signal sequence of 20 amino acids, pro-region of 44 amino acids and both of these are cleaved off to produce a mature form of the enzyme, which starts at position 65 of the protein encoded by the wild type of cDNA. Mature chicken cathepsin D starts with aminoacid residue 64. Human cathepsin E starts with amino acid 54. Some fungus aspartyl proteases start with amino acids 92 and 89. Thus, there is a variability as to the amino acid residue which is N-terminus of the mature form the aspartyl proteases of eukaryotic origin. In conclusion it was not obvious at the time of filling of the instant application that the disclosed aspartyl protease of SEQ ID NO: 2 may have its about 45 N-terminal amino acids cleaved off in the maturation process. Thus, one having skills in the art would not be motivated to obtain an active, recombinantly produced human beta-secretase by simple truncation of the first N-terminal 45 amino acids. In conclusion, the use of Tung et al. article was not proper and rejection of claims 1, 15, 18 and dependent claims 22 and 132-134 under 35 USC, section 103 is withdrawn.

Rejection of claims 23-25, 29-31, 33-34 and 36 which was maintained in the Advisory Action of January 19, as being unpatentable over US Patent 6,420,534, issued

to Gurney et al., with priority to the provisional application 60/101,594 filed Sept. 24, 1998, in view of the common knowledge in molecular biology and in the field of aspartyl proteases as exemplified by the review article by Tang J. et al. (Evolution in Structure and Function of Aspartyl Proteases, Journal of Cellular Biochemistry, 1987, 33, 53-63) and further in the view of the article by Viswandhan V. et al. (An Approach to Rapid Estimation of Relative Binding Affinities of Enzyme Inhibitors: Application to Peptidomimetics Inhibitors of the Human immunodeficiency Virus Type 1 protease, J. Med. Chem. 1996, 39, 705-712) **is withdrawn now**. The reasons for withdrawal of this rejection are explained above in withdrawal of rejection of claims are 1, 15, 18 and dependent claims 22 and 132-134.

2. Withdrawal of double patenting rejection

The non-provisional obviousness-type double patenting rejections of claim 1, over claims 1, 2, and 6 of US Patent No. 5,744,346, filed 01/28/1997, is withdrawn after reconsideration of provisional applications and the state of art in human beta-secretase. Although the claims previously rejected read on the purified, native, mature form of human beta-secretase which comprises amino acids 46-501 of SEQ ID NO: 2, SEQ ID NO: 2 is not the only allelic form of human beta secretase. For example, US Patent No. 6,319,689, filed 01/28/1997, issued to Powell et al. Nov. 2001, discloses human beta-secretase having in position 130 glutamine and not valine as in SEQ ID NO: 2 of the instant Application. Thus, it was not obvious at the time of filing that the protein

consisting of amino acid 46-501 of SEQ ID NO: 2 had been disclosed by the US Patent No. 5,744,346.

3. Examiner's amendment

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

In the specification

Please replace the Cross Reference to Related Applications section with the following replacement section.

> This application is a continuation of U.S. Application No. 09/501,708 filed January 10, 2000, now abandoned, which is a continuation-in-part of U.S. Application No. 09/471,669 filed December 24, 1999, both of which claim the benefit of U.S. Provisional Application numbers 60/114,408, filed 12/31/1998, 60/119,571 filed 2/10/1999 and 60/139,172 filed 6/15/99. Applications 09/501,708, 60/119,571 and 60/139,172 are hereby incorporated herein by reference in their entireties.

In the claims

(i) Please cancel claim 132.

(ii) Please amend claims 1 and 22 as follows.

1. A protein purified to apparent homogeneity comprising residues 63-452 of SEQ ID NO: 2, wherein the protein lacks amino acid residues 1-45 of SEQ ID NO: 2, and the protein exhibits β-secretase activity, and wherein the protein is recombinantly expressed [from a bacterial source].

22. The protein of claim 1, wherein said protein is produced from bacterial source [by a heterologous cell].

(iii) Please add claim 135.

135. The crystalline protein composition of claim 23, wherein said protein is deglycosylated.

Authorization for this examiner's amendment was given in a telephone interview with Applicants representative Joe Liebeschuetz on March 20, 2006.

4. Conclusion

Claims 1, 15, 18, 22, 23-25, 31, 33-34, 36 and 133-135 are allowed.

The following is the examiner's reason for allowance. Applicants discloses human beta-secretase of SEQ ID NO: 2 and encoding DNA sequence of SEQ ID NO: 1. The enzyme is participating in pathology of Alzheimer disease, therefore is of great clinical importance. Although SEQ ID NO: 2 was disclosed by Gurney et al. several month earlier than by the present Inventors (US Patent 6,420,534 having priority to provisional application 60/101,594, filed 09/24/1998), Gurney at al. have not

demonstrated that active beta-secretase produced in human brain has N-terminal amino acid in position of 46 of SEQ ID NO: 2. In addition, the patent does not teach that recombinant active forms of the enzyme may have as N-terminal position any of residues 22, 46, 58, or 63. Different isoforms of beta-secretase disclosed by Applicants may be used in screening for beta-secretase inhibitors, potential therapeutics decreasing amyloid plaque formation in brains of patient suffering from Alzheimer disease. The method of use of the disclosed forms of beta-secretase, claimed in the parallel application 09/724,571, has been already allowed.

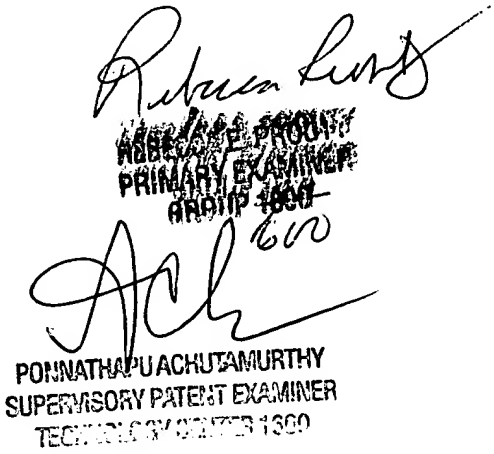
Any comments considered necessary by applicant must be submitted no later then the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Malgorzata A. Walicka whose telephone number is (571) 272-0944. The examiner can normally be reached on Monday-Friday from 10:00 a.m. to 4:30 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached on (571) 272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for

published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Malgorzata A. Walicka, Ph.D.
Art Unit 1652
Patent Examiner



Continuation of Attachment(s) 9. Other: copies of Fig 4 and 8 of the provisional application 60/114,408, copy of the articles in 892.

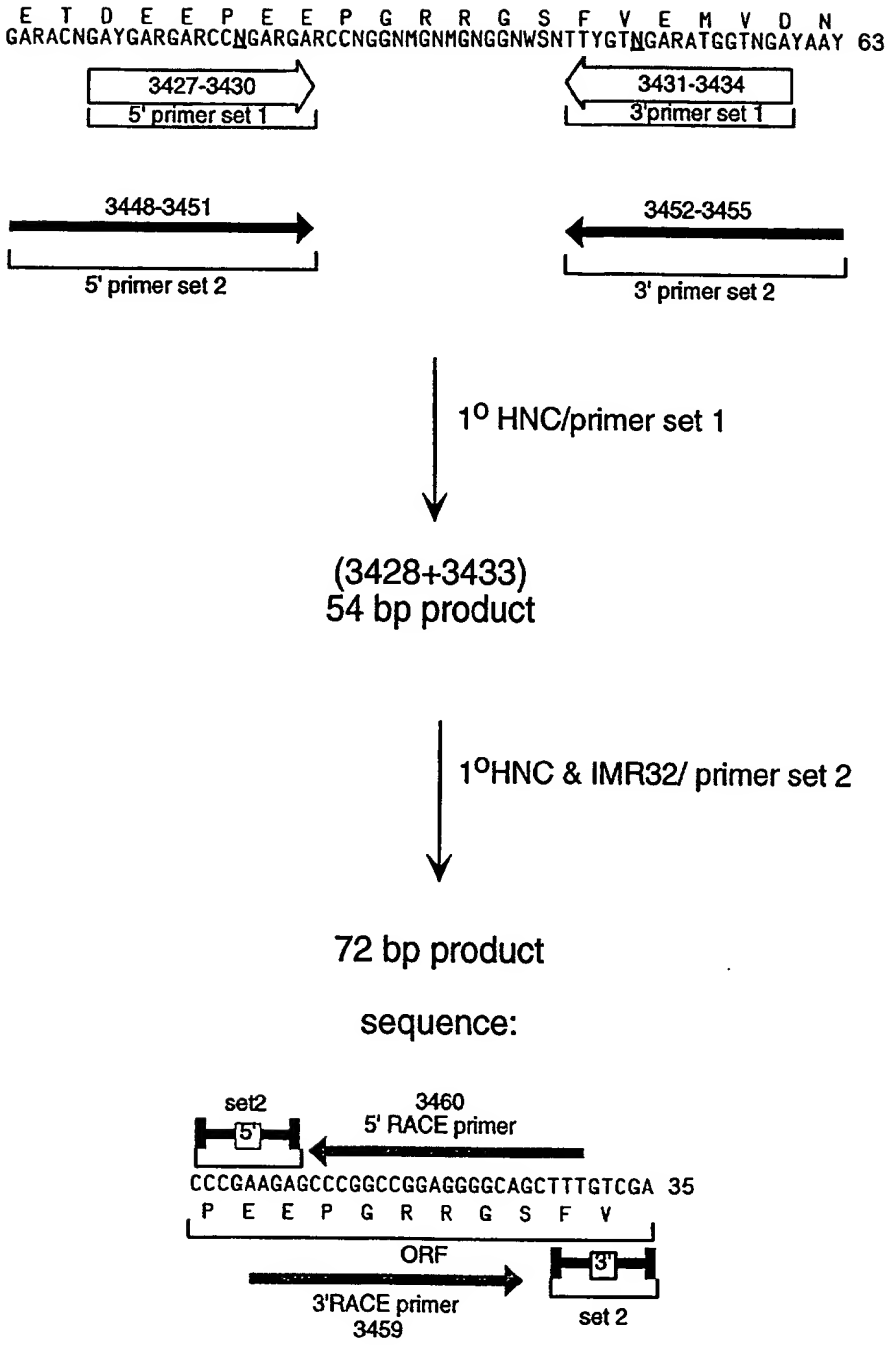

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FIG. 4

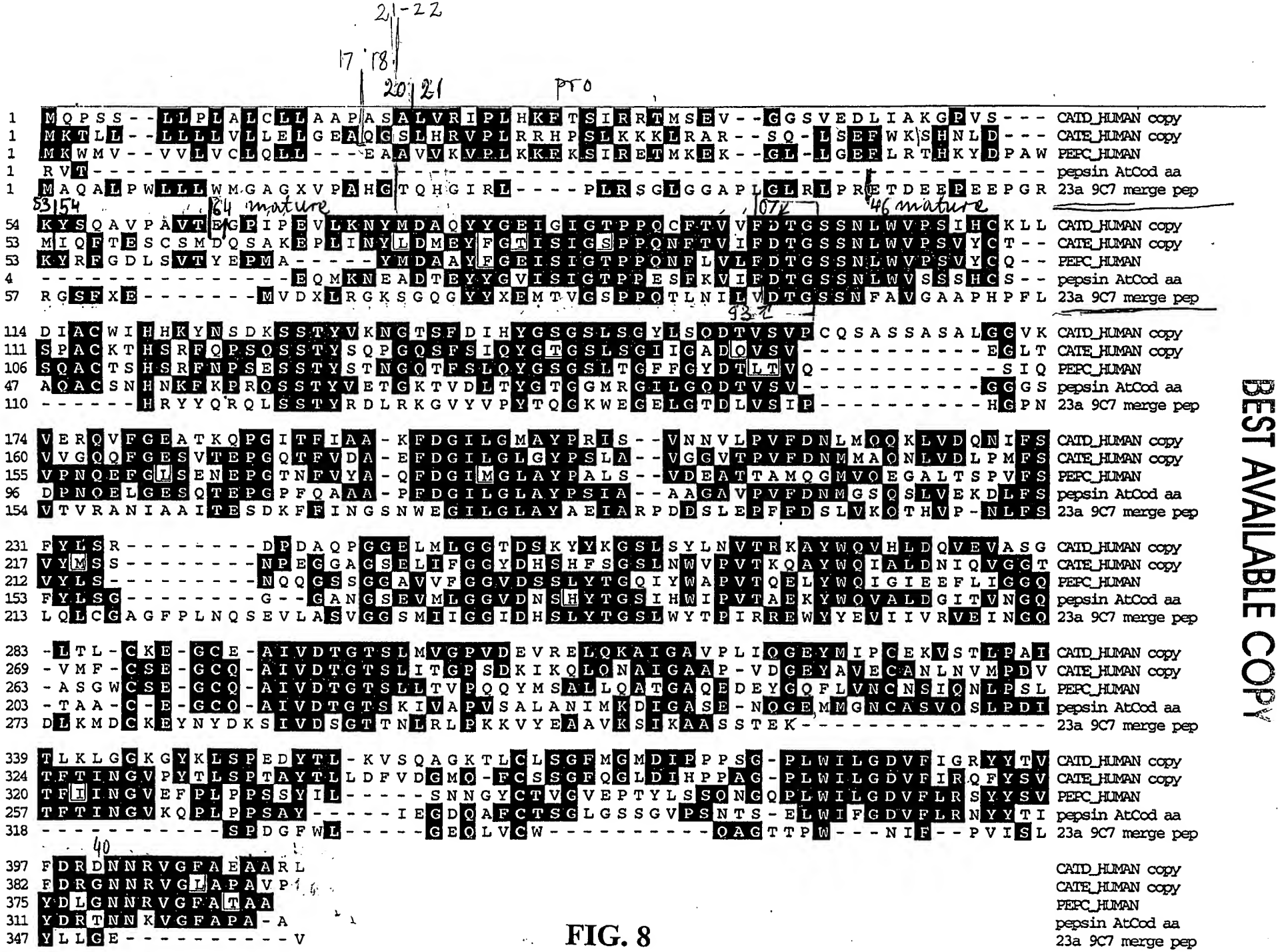

FIG. 8